REMARKS

This submission is in response to the Official Action dated December 2, 2002. New claim 42 has been added. Support for the claim can be found on page 6, lines 1-8 of the specification. Therefore, claims 29, 31-33, 35, 37, 38, 40, and 42 are pending. The specification has been amended on page 1 to correctly identify the reference to the priority PCT application. No new matter is added by these amendments. Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested.

Rejection of Claims 29, 31-33, 35, 37-38, and 40 For Lack of Enablement

The Examiner maintains the rejection of claims 29, 31-33, 35, 37-38 and 40 under 35 U.S.C. 112, ¶1 for lack of enablement for reasons of record. Specifically, the Examiner states that "the method of the instant claims must be enabled for its intended use, i.e., the treatment of a human, T cell-mediated autoimmune disease, in particular, MS. ...the method of the instant claims must be considered at best, highly unpredictable." The Examiner asserts that the "mechanisms are irrelevant as the methods of the instant claims have so far proven to be non-functional in humans."

The rejection is traversed, and reconsideration is respectfully requested.

It is applicants' position that the specification of the present invention is enabling for methods of the presently claimed invention, which is not directed to a cure of autoimmune diseases, nor to treatment of an autoimmune disease as might

have been defined by endpoints or differences from placebo in a clinical trial. Rather, both previously presented claims 29 and 35 and new claim 42 are limited to suppression of an autoimmune response. Specifically, applicants respectfully submit that the subject patent application contains evidence that would establish that the proposed oral regime would and does suppress an abnormal autoimmune response not only associated with multiple sclerosis but also with rheumatoid arthritis and any other T cell-mediated or T cell-dependent autoimmune disease.

In Examples 8 and 10 of the application, for example, the data support that adoptive transfer of protection against autoimmune diseases can be achieved using lymph node cells (LNC) obtained from tolerance-induced donors. Furthermore, the present invention identified the probable suppressor mechanism that could be mobilized by oral administration of a target tissue autoantigen. The mechanism itself provides the justification for extrapolating to abnormal autoimmune responses associated with many diseases. If the mechanism is active suppression (i.e., suppression of autoimmune response through elicitation of suppressor T cells in the gut), which is supported by Examples 11, 13, and 15, then oral tolerance would be likely to work in this class of human autoimmune diseases for several reasons including the following. First, even individuals with multiple sclerosis (or another autoimmune disease) are successful in orally tolerizing themselves to antigens in food, so the fact that patients' immune systems are dysfunctional would not be a deterrent to applying this regime to humans. Second, if the mechanism is active

suppression, effectiveness of the regime no longer depends on a hypothesis that T cells reactive with myelin basic protein mediate multiple sclerosis in humans or that T cells reactive with another particular self-antigen mediate rheumatoid arthritis in humans. The Examples represent the fact that these diseases are perpetrated by harmful T-cells activated against the tissues under attack. Support for this in human disease is presented in Burns et al., Cellular Immunology 1983, 81:435, at page 439 (See Exhibit A).

Further in Example 6, it is shown that fragments of MBP that are themselves incapable of inducing EAE disease are nevertheless successful when orally administered in abating the autoimmune response to MBP. In other words, oral administration of these fragments suppresses T cells that mediate the disease even though those T cells do not recognize the portion of the MBP molecule represented by the fragment. It is also significant that the rats of Example 6 did not already have EAE nor any other exposure to immunization with MBP prior to their being fed one of the non-disease inducing MBP fragments 1-37 and 90-170. This removes the possibility that prior exposure to the antigen would have somehow primed or prepared the rats for being tolerized with the fragment of the antigen. Example 6 then shows that oral tolerance in autoimmune disease is a phenomenon independent of the particular autoimmune disease (since the rats had no autoimmune disease before feeding) and that it does not require administration of the same antigen as the antigen recognized by the harmful T cells that mediate the disease.

Example 4 and Tables II and III demonstrate that it is not necessary to feed antigen prior to the beginning of autoimmunity. From the data of Examples 4 and 6, it clearly follows that T cells mediating the autoimmune disease can be suppressed or neutralized by oral administration of an autoantigen which need not be the same as the antigen to which these harmful T cells are sensitized. Since the fed antigen need not be the same as the inducing antigen, the generality of the oral tolerance phenomenon was established in just one disease model, and the issue of the breadth of the present claims is thereby resolved.

The specification also offers direct proof that the same oral tolerance treatment would work for rheumatoid arthritis, which is another autoimmune disease and one different from multiple sclerosis. Example 7 shows that feeding Mycobacterium tuberculosis (a constituent of complete Freund's adjuvant) to rats before induction of arthritis by immunization of the rats with complete Freund's adjuvant suppresses disease in the fed rats. Adjuvant-induced arthritis, the animal model used in Example 7, is a well-accepted model for rheumatoid arthritis and Mycobacterium tuberculosis is considered to be a "mimic" (i.e., the equivalent) of an autoantigen. See, e.g., Van Eden W. et al., Holoshitz, J., Nevo, Z., Frenkel, A., Klajman, A., Cohen, I.R., 1985, "Arthritis induced by a T lymphocyte clone that responds to Mycobacterium tuberculosis and to cartilage proleoglycans" Proc. Natl Acad. Sci. (USA), 82:5117-5120. (Exhibit B) This study demonstrates that a key antigen in Mycobacterium tuberculosis responsible for arthritis is cross-reactive

immunologically with self-cartilage. Thus, Mycobacterium tuberculosis presents a self-antigen related to joint cartilage. This is why, while technically not a "self" antigen, Mycobacterium tuberculosis induces a disease with immunological characteristics and clinical symptoms of the autoimmune disease rheumatoid arthritis. Because of this, Example 7 is a valid showing that the suppression of autoimmune response would work for the autoimmune disease rheumatoid arthritis.

The Examiner has also commented directly to the inclusion of poison ivy in the specification. Applicants submit that if the Examiner would prefer, reference to "poison ivy" may be removed from the specification. Applicants hereby expressly disclaim that poison ivy is a T-cell mediated autoimmune disease or involves an autoimmune response. The subject matter of poison ivy has been canceled from the claims.

The clinical trials to which the Examiner refers did not measure autoimmune response but rather a group of macroscopic observational parameters. Moreover, one clinical trial for rheumatoid arthritis succeeded, see, Barnett et al., Arthritis and Rheumatism 1998, 41(2): 290-297, of record.

Applicants respectfully submit that the above showing of support in the specification supports the presently claimed methods in animals and humans. Therefore, applicants respectfully submit that the rejection be withdrawn.

Rejection of claims 29, 31-33, 35, 37-38, and 40 as New Matter

Claims 29, 31-33, 35, 37-38, and 40 stand rejected under 35 U.S.C. 112, ¶ 1 as new matter. The Examiner contends that the language in claims 29, 35, and 37 is unsupported by the specification as filed. With respect to claims 29 and 35, the Examiner asserts that "suppressing an autoimmune response ... in a human presenting with said autoimmune response" is not supported. In addition, with respect to claim 37, the Examiner states that "wherein said autoantigen is bovine myelin basic protein" is also not supported by the specification. The rejection is traversed, and reconsideration is respectfully requested.

Applicants have reviewed the previous response and note that the amendments to claims 29, 35, and 37 added no new matter to the application. The applicants failure to assert the presentation of no new matter was a clear oversight that is addressed by the preceding sentence and with the following discussion of support from the specification.

With respect to claims 29 and 35, the previous amendments read as follows:

> 29. (Amended) A method for the treatment of a T cell-mediated or T cell-dependent autoimmune disease by suppressing an autoimmune response associated with said disease in a human [suffering from] presenting with said autoimmune [disease] response, said method comprising orally or enterally administering to said human at least one antigen in an amount effective to suppress said autoimmune response, said antigen selected from the group consisting of autoantigens specific for said autoimmune disease, said suppression comprising

elicitation of suppressor T cells specific to said administered antigen.

35. (Amended) A method of treating a T cell-mediated or T cell-dependent autoimmune disease by suppressing an autoimmune response associated with said disease in a human [suffering from] presenting with said autoimmune [disease] response, said method comprising orally or enterally administering to said human at least one antigen in an amount effective to suppress said autoimmune response, said antigen selected from the group consisting of autoantigens specific for said autoimmune disease.

Support for these amendments can be found throughout the specification, including page 1, lines 24-26 reading as follows (emphasis added):

> Autoimmune diseases are caused by an abnormal immune response involving either cells or antibodies directed against normal tissues. A number of strategies have been developed to suppress autoimmune diseases, most notably drugs which nonspecifically suppress the immune response.

Therefore, the treatment is directed to humans who have ongoing abnormal autoimmune response, and therefore, humans who "present with" the immune response associated with the autoimmune disease.

The Examiner has also pointed out that "A review of the Examples indicates that in most cases the treatment is administered before the induction of the disease, thus, there was no treatment after presentation." Applicants respond by pointing out Examples 4 and 6, and Table II and III at pages 18-19, where administration of antigen occurs after the induction of disease, and yet suppression is achieved.

Furthermore, applicants respectfully direct the Examiner to MPEP 2164.02, which reads,

> An applicant need not have actually reduced the invention to practice prior to filing. In Gould v. Quigg, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), as of Gould's filing date no person had built a light amplifier or measured a population in inversion in a gas discharge. The Court held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting In re Chilowsky, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)).

MPEP 2164.02 also states that, "because only an enabling disclosure is required, applicant need not describe all embodiments." Here, by contrast, two separate embodiments, pre-induction and post-induction, have been described and exemplified.

As we stated above in addressing the enablement rejection, the claimed regime involves tolerization of the abnormal T cells and therefore its operativeness is expected even based solely on experiments that administer antigen before induction of disease. Therefore, applicants submit that the remaining examples in the present invention which relate to particular pre-induction embodiments, also support the claimed invention.

Applicants also rely on Example 6, <u>in part</u>, for support of previously amended claim 37 which reads,

> 37. (Amended) The method of claim 35 wherein said <u>disease is multiple sclerosis and said</u> autoantigen is bovine myelin basic protein.

The Examiner has stated that "Said example does not provide support for treating MS by administering bMBP. Said example merely discloses that bMBP can inhibit the induction of EAE in rats if fed ... before induction of disease." Applicants submit that Example 6 demonstrates (i) that bovine myelin basic protein is administered to abate abnormal immune response associated with an autoimmune disease model, specifically EAE, and (ii) that this model is widely used for multiple sclerosis, and (iii) that suppression of autoimmune response is not being claimed prior to the start of the abnormal autoimmune response. Note that all independent claims require the treated subject to "present with" i.e., have ongoing autoimmune response. If Example 6 is not sufficient, the Examiner's attention is directed to Example 4 (discussed above).

MBP is specifically identified as an autoantigen at page 8, line 10. Moreover, it has also been identified as the inducing antigen in EAE ("the antigen to which the T-cells that mediate the disease are sensitized" at page 7, lines 31-32). In turn, the specification, in more than one location, states that EAE is a known model for multiple sclerosis. For example, on page 2, lines 7-10, and on page 7, lines 11-14, the specification states,

> EAE is a T cell-mediated autoimmune disease directed against myelin basic protein (MBP) and has been studied as a model for multiple sclerosis in several mammalian species.

Since applicants have disclosed MBP as an autoantigen and stated that it induces EAE, and that it is a model for multiple sclerosis, it follows that MBP is considered an autoantigen for MS.

In view of the foregoing support in the specification discussed above for the previous amendments to claims 29, 35, and 37, applicants respectfully submit that no new matter is added by these previous amendments, and that the rejection on these grounds should be withdrawn.

Double Patenting Rejections

The Examiner has also rejected claim 37 under the doctrine of obviousness-type double patenting. Applicants herewith submit a terminal disclaimer in view of U.S. Patent 5,869,054 and U.S. Patent 6,036,957 upon a finding of allowable subject matter.

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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